

PATENT

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Attorney Docket No. AFFY-003/26US

Application No. 10/694,541

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Stephen P.A. FODOR *et al.*

Confirmation No.: 3654

Application No.: 10/694,541

Group Art Unit: 1634

Filed: October 28, 2003

Examiner: Jeanine A. Goldberg

For: Arrays for Detecting Nucleic Acids

Commissioner for Patents
U.S. Patent and Trademark Office
Customer Service Window, Mail Stop Amendment
Randolph Building
401 Dulany Street
Alexandria, VA 22314

INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. §1.97(b)

In accordance with the duty of disclosure set forth in 37 C.F.R. §1.56,
Applicant(s) hereby submits the following information in conformance with 37 C.F.R. §§1.97
and 1.98.

☒ Pursuant to 37 C.F.R. §1.98, copies of documents 1-5, 47, 48, 122-694 cited in the attached Form PTO-1449 are enclosed. **Copies of these documents may be found in the accompanying four (4) boxes submitted with this information disclosure statement. For the Examiner's convenience, the documents have been arranged within the boxes in the exact order in which they have been listed in the PTO-1449 forms submitted herewith.**

☐ Copies of the remaining publications listed on the attached Form PTO-1449 are not being provided pursuant to 37 C.F.R. §1.98(d) because the publications were previously cited by or submitted to the Office in prior Application Serial Nos.: to which the above-identified application claims priority under 35 U.S.C. §120.

☐ Copies of documents that were not submitted in the above-mentioned related United States Patent Applications may be found in related United States Patent Application Nos.:

Should the Examiner be unable to locate a document, a copy will be provided upon request.

- ☒ No copies of any U.S. patents or U.S. patent application publications listed on the attached Form PTO-1449 are being provided pursuant to 37 C.F.R. §1.98.
- ☐ Documents _____ were cited by the Examiner in an Office Action mailed _____, in Applicants' related U.S. Application no. _____.
- ☐ Document _____ was cited in an IDS and submitted to the Office in several of Applicants' pending related U.S. Applications.
- ☒ Applicants understand that MPEP § 2001.06(c) only requires disclosure of litigation where the subject matter for which a patent is being sought is or has been involved in litigation. Applicants will work with the Examiner to determine what particular information from any given litigation might be relevant to the instant application, if any. Given that opponents of Affymetrix (the assignee of the instant application) have sought in the past and may seek in the future to expand the scope of the requirements under the MPEP, Applicants herein provide the Examiner with an overview of all potentially relevant litigation and other *inter partes* proceedings so that the Examiner may also make independent determinations in that regard.
- ☒ Affymetrix, the assignee of the instant application, was a party in three patent infringement actions originally filed in 1998. *Affymetrix, Inc. v. Hyseq, Inc.*, was filed in the Northern District of California on August 18, 1998, and given the docket number 98cv3192 FMS. U.S. Patents 5,744,305, 5,800,992 and 5,795,716 (the "the '305 patent," "the '992 patent," and "the '716 patent," respectively) were asserted in this litigation. Upon reassignment of the case to Judge Fogel, Northern District of California (San Jose Division), the case was renumbered as 99cv21163. The '305 patent generally claims arrays of nucleic acids comprising at least 400 different nucleotides/cm². The '992 patent generally claims methods of detecting nucleic acids in two or more collections of nucleic acids. The '716 patent generally claims computer program products and systems for identifying an unknown base in a sample. Appendix A contains the independent claims of each patent.

The instant application (U.S. application no. 10/125,428) is a continuation of application Ser. No. 09/670,563, filed Sep. 27, 2000; which is a continuation of application Ser. No. 09/362,089, filed Jul. 28, 1999; which is a divisional of application Ser. No. 09/056,927, filed Apr. 8, 1998, pending; which is a continuation of application Ser. No. 08/670,118, filed Jun. 25, 1996, now U.S. Pat. No. 5,800,992. The instant application and U.S. Patent 5,744,305 share a common parent application in U.S. application no. 07/492,462, now abandoned. U.S. Patent 5,795,716 is not related by priority claim to the instant application.

Affymetrix, Inc. v. Synteni, Inc., and Incyte Pharmaceuticals, Inc., Civil Docket No. 98cv6 GMS, was filed in the District of Delaware on January 6, 1998. In this case, U.S. Patent 5,445,934 (the '934 patent) was asserted. Upon transfer to the Northern District of California (San Francisco Division), the case was renumbered 98cv4507. Upon reassignment of the case to Judge Fogel, Northern District of California (San Jose Division), the case was renumbered 99cv21164. The '934 patent generally claims substrates and arrays of oligonucleotides at different densities. Appendix B contains the independent claims of the patent. The instant application and U.S. Patent 5,445,934 share a common parent application in U.S. application no. 07/492,462, now abandoned.

The third case, *Affymetrix, Inc. v. Synteni, Inc., and Incyte Pharmaceuticals, Inc.*, Civil Docket No. 98cv520 JJF, was filed in the District of Delaware on September 1, 1998. It was later assigned to GMS. In this case, the '305 and '992 patents were asserted. Upon transfer to the Northern District of California (San Francisco Division), the case was renumbered as 98cv4508. Upon reassignment of the case to Judge Fogel, Northern District of California (San Jose Division), the case was renumbered as 99cv21165. Appendix A contains the independent claims of each patent.

In the course of the above described litigations, Incyte and Synteni alleged that at least the '992 patent was invalid and unenforceable due to lack of enablement under 35 U.S.C. § 112, first paragraph. Incyte and Synteni submitted as evidence, a declaration from Dr. Michael C. Pirrung (document 176 in the attached Form 1449). Dr. Pirrung is an inventor of the instant pending claims. The declaration specifically pertains to US Patent 5,800,992, and is potentially material to the prosecution of the claims of the instant application as it conveys Dr. Pirrung's opinion regarding non-enablement of the VLSIPS method of nucleic acid synthesis, which is one disclosed method that may be used to make the claimed beads. Equally relevant, however, are Document Nos. 177- 179 in the attached Form 1449 from the same litigation (declarations of Fodor, Leighton Read and Stryer) which discuss Dr. Pirrung's limited involvement in the nucleic acid synthesis program at Affymetrix as well as his strained relationship with the Affymetrix scientists.

For instance, as stated in Document 177 at paragraphs 5-6 (Fodor declaration):

Dr. Pirrung left Affymax [(Affymetrix)] towards the end of 1989, apparently to take up an academic position at Duke University. Since that time, Dr. Pirrung has had only occasional contact with my research group at Affymax. He has not been involved with my research group in any experimental work to develop nucleic acid arrays at Affymetrix or Affymax.

Similarly, as stated in Document 178 at paragraph 11 (Leighton Read declaration):

I am not aware that Dr. Pirrung had any direct participation in experimental work relating to DNA arrays much after the first US priority patent application filing in June 1989, at Affymax. I also have no reason to believe that Dr. Pirrung was aware of the details of experimental work on DNA arrays, and in particular the results being obtained, after he left Affymax. It is not at all clear to me, therefore, that Dr. Pirrung would have any first-hand knowledge of the detail of the results or conclusions being drawn at Affymax in 1990 as he purports to discuss in his declaration.

With regard to the relationship between Drs. Fodor and Pirrung, Dr. Stryer states, "I was aware as early as 1990 that the professional relationship between Dr. Fodor and Dr. Pirrung was strained" (Document 179 at 6) (Stryer Declaration). Dr. Leighton Read also recollects on the strained relationship between Drs. Fodor and Pirrung in her declaration (Document 178 at 7-10), and particularly the apparent jealousy exhibited by Dr. Pirrung toward the success of Dr. Fodor. For instance, she states, "By late 1989, Dr. Pirrung was seemingly getting increasingly frustrated at the success of Dr. Fodor and his work . . . Although Dr. Pirrung was trying to stake a claim in the field after leaving Affymax, it was Dr. Fodor who received the greatest public attention" (Document 178 at paragraphs 8 and 10).

Also relevant are documents 661 and 662 (Board Decisions in Interferences 104,358 and 104,359), which show that on at least two occasions the Board of Patent Appeals & Interferences has determined that Pirrung's work, in fact, supported enablement (details of these two interferences are discussed below). In particular, they found that a 1995 article by Pirrung discussing problems with light-directed, solid-phase DNA synthesis supported enablement:

Perfection or optimization of an invention, however is not a requirement of enablement. [Cite omitted.] Nowhere does Pirrung state that the light-directed method of synthesis will not work. In fact, Pirrung states that light-directed synthesis is advantageous for preparing large, high density arrays of polymer sequences to enable sequencing-by-hybridization.

Document No. 661 at 10 and Document No. 662 at 11. In both cases, the Board concluded that Incyte had "failed to establish a threshold case by a preponderance of the evidence that Fodor's disclosure would not have enabled one skilled in the

art to make and use the claimed invention.” Document No. 661 at 11 and Document No. 662 at 11.

- [x] The above described litigations were settled by the parties. Before settlement, a motion for partial summary judgment of claims 1-3 of the ‘992 patents was granted, rendering said claims invalid in relation to the term “substantially complementary.”
- [x] Applicants bring the following additional information to the Examiner's attention pending Civil Action No. 04-901-JJF in the U.S. District Court for the District of Delaware. Applicants note that this civil action involves multiple patents, including U.S. Patent Nos. 5,545,531; 5,795,716; 6,355,432; 6,399,365; 6,646,243 and 6,607,887, owned by the assignee of this application, and the action is stylized as Affymetrix v. Illumina. The claims of the ‘432 patent and some of the claims of the ‘243 patent are generally directed to collections of encoded beads which have binding polymers of different target specific sequence attached thereto or to substrates comprising beads, spheres or particles comprising nucleic acids attached thereto. The asserted claims of the litigation are listed in Appendix C

The following references have been cited by Illumina as relevant to the patentability of various “bead” and other claims under 35 U.S.C. §§ 102 or 103 (a copy of Defendant Illumina, Inc.’s Identification of Invalidity Defenses Pursuant to 35 U.S.C. § 282 is attached as Exhibit 20):¹

Asserted claims 2, 5, 8, and 9 of US 6,355,432 are alleged to be invalid under 35 U.S.C. § 102 and 103 based on:

- EP 0392546
- Crkvenjakov et al. “Miniaturization of Sequencing by Hybridization (SBH): A Novel Method For Genome Sequencing” abstract no. P37, DOE/NIH Human Genome Contractors/Grantee Workshop (Nov. 1989)
- Drmanac / Crkvenjakov et al. “Miniaturization of Sequencing by Hybridization (SBH): The ‘Sequencing Chip’ Concept” 19 pages, poster, exact publication date in 1989 and source unknown
- Crkvenjakov, R. and R. Drmanac, “An Integral Approach for Complex Genome Studies,” research proposal submitted Office of Health and Environmental Research, U.S. Department of Energy, 54 pages (Oct. 1990)

¹ The following references are provided in the attached Form 1449, or have been previously cited in the instant collection.

- Drmanac, R., et al., "Towards Genome DNA Sequencing Chip Based on Oligonucleotide Hybridization," 2 pages, publication date and source unknown
- Drmanac et al., "Prospects for a Miniaturized, Simplified and Frugal Human Genome Project," Sci. Yugoslav. 16(1-2):97-107 (1990)
- Drmanac, R., et al., "Prospects For Miniaturized, Simplified And Frugal Human Genome Project: The 'Sequencing Chip' Concept," 10 pages, publication source unknown (Oct. 1989)
- Drmanac, R., et al., "Sequencing by Oligonucleotide Hybridization: A Promising Framework in Decoding of the Genome Program?" The First Intl. Conf. Electrophoresis, Supercomputing, and the Human Genome, Eds. Cantor and Lim, World Scientific, pp. 47-59 (Apr. 10-13, 1990)
- Crkvenjakov, Talk presented at DOE/NIH Human Genome Sequencing Conference in Santa Fe, NM
- Crkvenjakov, "Sequencing of Megabase Plus DNA by Hybridization: Method Development ENT," Excerpts from DOE Grant No. DE-FB02-88ER60699, 18 pages (October 1990)

Asserted claims 2 US 6,355,432 are alleged to be invalid under 35 U.S.C. § 102 and 103 based on:

- US 5,219,763

Asserted claims 2, 5, 8, and 9 of US 6,355,432 are alleged to be invalid under 35 U.S.C. § 103 based on:

- CA 1248873 in combination with EP 0392546
- GB 1561042 in combination with EP 0392546
- US 5,028,545 in combination with EP 0392546
- US 5,291,763 in combination with EP 0392546

Asserted claims 2, 5, and 8 of US 6,355,432 are alleged to be invalid under 35 U.S.C. § 103 based on:

- CA 1248873 in combination with US 5,348,855
- GB 1561042 in combination with US 5,348,855

Asserted claims 14, 16, 18, 19, 20, 21, 22, 24, 26, 35, 36, 39, 40, and 43 of US 6,646,243 are alleged to be invalid under 35 U.S.C. § 102 and 103 based on:

- Stodolsky, M., "Sequencing By Hybridization (SBH) The Rasomir Crkvenjakov Laboratory in 1989," 4 pages, (June 1989)

- Drmanac, R., et al., "Prospects For Miniaturized, Simplified And Frugal Human Genome Project: The 'Sequencing Chip' Concept," 10 pages, publication source unknown (Oct. 1989)
- EP 0392546
- Drmanac, R., et al., "Towards Genome DNA Sequencing Chip Based on Oligonucleotide Hybridization," 2 pages, publication date and source unknown
- Drmanac, R., et al., "Sequencing by Oligonucleotide Hybridization: A Promising Framework in Decoding of the Genome Program?" The First Intl. Conf. Electrophoresis, Supercomputing, and the Human Genome, Eds. Cantor and Lim, World Scientific, pp. 47-59 (Apr. 10-13, 1990)
- Drmanac / Crkvenjakov et al. "Miniaturization of Sequencing by Hybridization (SBH): The 'Sequencing Chip' Concept" 19 pages, poster, exact publication date in 1989 and source unknown
- Stodolsky, "Sequencing by Hybridization (SBH) R&D at the Center for Genetic Engineering in Belgrade, Yugoslavia: The Radomir Crkvenjakov Laboratory in 1989," 6 pages, (publication location and exact date in 1989 unknown)

Asserted claims 14, 16, 18, 19, 20, 21, 22, 24, 26, 35, 36, 39 and 40 of US 6,646,243 are alleged to be invalid under 35 U.S.C. § 102 and 103 based on:

- Crkvenjakov, R. and R. Drmanac, "An Integral Approach for Complex Genome Studies," research proposal submitted Office of Health and Environmental Research, U.S. Department of Energy, 54 pages (Oct. 1990)

Asserted claims 14, 15, 18, 19, 20, 21, 22, 24, 26, 35, 39, 40, and 43 of US 6,646,243 are alleged to be invalid under 35 U.S.C. § 102 and 103 based on:

- US 5,700,637

Asserted claims 14, 15, 16, 18, 19, 20, 21, 22, 24, 26, 35, 36, 39, and 40 of US 6,646,243 are alleged to be invalid under 35 U.S.C. § 102 and 103 based on:

- Drmanac et al., "Prospects for a Miniaturized, Simplified and Frugal Human Genome Project," Sci. Yugoslav. 16(1-2):97-107 (1990)

Asserted claims 14, 15, 19, 20, 21, 22, 26, 35, 39, 40 and 43 of US 6,646,243 are alleged to be invalid under 35 U.S.C. § 102 and 103 based on:

- Drmanac, R., et al., "Prospects For Miniaturized, Simplified And Frugal Human Genome Project: The 'Sequencing Chip' Concept," 10 pages, publication source unknown (Oct. 1989)

Asserted claims 14, 15, 16, 18, 19, 20, 21, 22, 24, 26, 35, 36, 39, and 40 of US 6,646,243 are alleged to be invalid under 35 U.S.C. § 103 based on:

- CA 1248873 in combination with US 5,028,545
- CA 1248873 in combination with EP 0392546
- CA 1248873 in combination with US 5,348,855

Asserted claims 14, 16, 18, 19, 20, 21, 22, 24, 26, 35, 36, 39, and 40 of US 6,646,243 are alleged to be invalid under 35 U.S.C. § 103 based on:

- EP 0392546 in combination with US 4,877,965

Asserted claims 14, 18, 20, 21, 26, 35, 36, 39, and 40 of US 6,646,243 are alleged to be invalid under 35 U.S.C. § 103 based on:

- EP 0392546 in combination with US 5,028,545

Asserted claims 1-4 of US 5,545,531 are alleged to be invalid under 35 U.S.C. § 102 and 103 based on:

- US 6,270,961
- US 5,807,522
- WO 93/17126
- US 6,103,463
- US 6,140,044
- Maskos, U., A Novel Method Of Nucleic Acid Sequence Analysis, Doctoral Thesis, Univ. of Oxford, 165 pages (1991)
- WO 95/09248
- Format 3 SBH Super Chip

Asserted claims 1, 5, and 9 of US 5,795,716 are alleged to be invalid under 35 U.S.C. § 102 and 103 based on:

- Southern et al., "Analyzing and Comparing Nucleic Acid Sequences by Hybridization to Arrays of Oligonucleotides: Evaluation Using Experimental Models" Genomics 13:1008-1017, Academic Press, San Diego, California (1992)
- Maskos, U. and E.M. Southern 'A Study of Oligonucleotide Reassociation Using Arrays of Oligonucleotides Synthesized on a Glass Support," Nucl. Acids Res. 21:4663-4669, Oxford University Press, Oxford, England (1993)
- Drmanac, R., et al., "SBH and the Integration of Complementary Approaches in the Mapping, Sequencing, and Understanding of Complex Genomes," The Second International Conference on Bioinformatics, Supercomputing and Complex Genome Analysis: Proceedings of the June 4-7, 1992 Conference at St. Petersburg Beach, Florida. pp. 121-134, (1993)

Asserted claims 10 of US 5,795,716 are alleged to be invalid under 35 U.S.C. § 103 based on:

- Southern et al., "Analyzing and Comparing Nucleic Acid Sequences by Hybridization to Arrays of Oligonucleotides: Evaluation Using Experimental Models" Genomics 13:1008-1017, Academic Press, San Diego, California (1992) in combination with US 5,171,534
- Maskos, U. and E.M. Southern 'A Study of Oligonucleotide Reassociation Using Arrays of Oligonucleotides Synthesized on a Glass Support," Nucl. Acids Res. 21:4663-4669, Oxford University Press, Oxford, England (1993) in combination with US 5,171,534

Asserted claims 1, 5, 9, and 10 of US 5,795,716 are alleged to be invalid under 35 U.S.C. § 102 and 103 based on:

- US 5,700,637
- Drmanac, R., et al., "DNA Sequence Determination by Hybridization: A Strategy for Efficient Large-Scale Sequencing," Science 260:1649-1652, American Association for the Advancement of Science, Washington D.C. (1993)
- Report on the Sequencing by Hybridization Workshop, Moscow, USSR (November 19-20, 1991)
- Mirzabekov, A.D., "DNA sequencing by hybridization--a megasequencing method and a diagnostic tool?," TIBTECH 12:27-32, Elsevier Science Publishers B.V., Amsterdam, The Netherlands (1994)
- Khrapko et al., "A method for DNA sequencing by hybridization with oligonucleotide matrix," DNA Sequence – J. DNA Sequencing and Mapping 1:375-388 (1991)
- Drmanac, R., et al., "Sequencing by Oligonucleotide Hybridization: A Promising Framework in Decoding of the Genome Program?" The First Intl. Conf. Electrophoresis, Supercomputing, and the Human Genome, Eds. Cantor and Lim, World Scientific, pp. 47-59 (Apr. 10-13, 1990)
- EP 0514927 A1

Asserted claims 1 and 5 of US 5,795,716 are alleged to be invalid under 35 U.S.C. § 102 and 103 based on:

- US 5,525,464
- US 5,202,231
- Elder, J.K., "Image Processing in Nucleic Acid Sequence Analysis," 166 pages, A thesis submitted for the degree of Doctor of Philosophy, University of Oxford (1993)

Asserted claims 9 and 10 of US 5,795,716 are alleged to be invalid under 35 U.S.C. § 102 and 103 based on:

- US 5,525,464 in combination with US 5,700,637

Asserted claims 1, 5, and 10 of US 5,795,716 are alleged to be invalid under 35 U.S.C. § 102 and 103 based on:

- Drmanac, R., et al., "Sequencing of Megabase Plus DNA by Hybridization: Theory of the Method" Genomics 4:114-128, Academic Press, San Diego, California (1989)
- Strezoska, Z., et al., "DNA sequencing by hybridization: 100 bases read by a non-gel-based methods," Proc. Natl. Acad. Sci. USA 88:10089-10093, National Academy of Sciences, Washington, D.C. (1991)
- Kreindlin et al., "A Sequenator for Analysis of Diagnostic and Sequencing Microchips," Int'l. Workshop on Sequencing by Hybridization, 2 pages (October 29-30, 1993)
- Lysov et al., "A New Method for Determining the DNA Nucleotide Sequence by Hybridization with Oligonucleotides," Abstract of Human Genome I: An International Conference on the Status and Future of Research on the Human Genome (October 1989)
- Mirzabekov, "Sequencing of DNA by Hybridization with oligonucleotides matrix (SHOM)," Engelhardt Institute of molecular Biology Grant Application (March 1992) ("Mirzabekov Grant Application, 1992")
- Khrapko et al., "Hybridization of DNA with Oligonucleotides Immobilized in Gel: A Convenient Method for Detecting Single Base Substitutions," Molecular Biology 25:581-591 (Dec. 1991) (Russian original: volume 25(3), pp. 718-730, May-Jun. 1991)
- US 4,811,218

Asserted claims 1, 5, and 10 of US 5,795,716 are alleged to be invalid under 35 U.S.C. § 103 based on:

- US 4,802,101
- US 5,332,666
- US 5,306,618
- US 5,171,534

Asserted claims 1, 2, 7, 10, 17, 20-22, 24, 27-32, 35-37, 41, 44, 45, 55, and 58 of US 6,399,365 are alleged to be invalid under 35 U.S.C. § 103 based on:

- US 5,143,854
- US 5,700,637

- Drmanac, R., et al., "SBH and the Integration of Complementary Approaches in the Mapping, Sequencing, and Understanding of Complex Genomes," The Second International Conference on Bioinformatics, Supercomputing and Complex Genome Analysis: Proceedings of the June 4-7, 1992 Conference at St. Petersburg Beach, Florida. pp. 121-134, (1993) in combination with GB 2129551
- US 4,159,875
- US 4,430,299
- US 4,039,288
- US 4,595,562
- US 4,608,231
- US 4,675,299
- US 4,676,951
- US 4,678,894
- US 4,719,087
- GB 2129551

Asserted claims 1 and 7 of US 6,607,887 are alleged to be invalid under 35 U.S.C. § 102 and 103 based on:

- US 5,700,637
- US 5,171,534
- Drmanac, R., et al., "Sequencing of Megabase Plus DNA by Hybridization: Theory of the Method" Genomics 4:114-128, Academic Press, San Diego, California (1989)
- Strezoska, Z., et al., "DNA sequencing by hybridization: 100 bases read by a non-gel-based methods," Proc. Natl. Acad. Sci. USA 88:10089-10093, National Academy of Sciences, Washington, D.C. (1991)
- Drmanac, R., et al., "DNA Sequence Determination by Hybridization: A Strategy for Efficient Large-Scale Sequencing," Science 260:1649-1652, American Association for the Advancement of Science, Washington D.C. (1993)
- Drmanac, R., et al., "SBH and the Integration of Complementary Approaches in the Mapping, Sequencing, and Understanding of Complex Genomes," The Second International Conference on Bioinformatics, Supercomputing and Complex Genome Analysis: Proceedings of the June 4-7, 1992 Conference at St. Petersburg Beach, Florida. pp. 121-134, (1993)
- Drmanac, R., et al., "Sequencing by Oligonucleotide Hybridization: A Promising Framework in Decoding of the Genome Program?" The First Intl. Conf. Electrophoresis, Supercomputing, and the Human Genome, Eds. Cantor and Lim, World Scientific, pp. 47-59 (Apr. 10-13, 1990)

- EP 0514927 A1
- Elder, J.K., "Image Processing in Nucleic Acid Sequence Analysis," 166 pages, A thesis submitted for the degree of Doctor of Philosophy, University of Oxford (1993)
- Report on the Sequencing by Hybridization Workshop, Moscow, USSR (November 19-20, 1991)
- Kreindlin et al., "A Sequenator for Analysis of Diagnostic and Sequencing Microchips," Int'l. Workshop on Sequencing by Hybridization, 2 pages (October 29-30, 1993)
- Mirzabekov, "Sequencing of DNA by Hybridization with oligonucleotides matrix (SHOM)," Engelhardt Institute of molecular Biology Grant Application (March 1992) ("Mirzabekov Grant Application, 1992")
- US 4,811,218

Asserted claims 1 and 5 of US 6,607,887 are alleged to be invalid under 35 U.S.C. § 102 and 103 based on:

- US 5,202,231

Illumina has also asserted that the '243 patent is invalid because of inequitable conduct in relation to the failure to disclose to the U.S. Patent Office the above described litigation against Hyseq, Synteni and Incyte, in particular litigation in relation to the '922 patent and the Pirrung declaration as described above. These assertions have been disputed by Affymetrix .

Should the Examiner wish to review any documents in applicants possession related to this action, the Examiner is invited to contact the undersigned and any documents requested will be forwarded.

[x] European Opposition Proceedings:

Affymetrix has been a party in the following European Opposition proceedings, wherein a granted Affymetrix European patent was challenged:

1. **EP 1086742**

Opponent: Degussa AG

Status: Decision issued on July 26, 2006 affirming maintenance of the patent based on amendments made during the opposition. A copy of the Grounds for Decision, Interlocutory Decision, Maintenance of the Patent papers are included as Form 1449 documents 185-187.

Claims: The amended claims as accepted by the EP opposition division are generally directed to the use of a constraining means on a substrate for defining regions to react with a reactant solution in the manufacture of polymer array. The amended claims are attached as Exhibit 1.

Issues: Allegations of lack of novelty and inventive step.

References cited:

WO 89/10977

US 4,728,591

Declaration of Grant Morgan, in Japanese Patent Application No. 8-324451, 15 pages (dated September 16, 2002)

US 5,700,637

Claims as granted of EP 834575, 2 pages, (November 28, 2001)

Interlocutory decision in Opposition proceedings, in the Opposition to EP 0834575, 33 pages (dated January 24, 2005)

Analysis of ECLA classification of D1 and D2, 3 pages (submitted August 8, 2005)

WO 93/09668

EP 0 624 059 A0

WO 90/15070

Fodor et al., "Light-directed, spatially addressable parallel chemical synthesis" Science 251:767-773, American Association for the Advancement of Science, Washington D.C. (1991)

EP 0 445 915 A1

US 4,834,946

2. EP 0834575

Status: Decision on maintenance of EP patent 0834575 issued on Jan. 24, 2005 based on amendments made during opposition proceedings. Decision on appeal pending. A copy of the Summary of Facts and Submissions, including preliminary opinion, Communication concerning Oral Proceeding Minutes, Interlocutory Decision, Summary of Facts and Submissions (dated January 24, 2005) and Notice of Appeal filed by Affymetrix are included as Form 1449 documents 192-196. Various other opposing parties appealed the same decision of the Opposition Division.

Claims: The amended claims as accepted by the EP opposition division are generally directed to methods for identifying target nucleic acids comprising providing an array of in excess of 100 different probes bound to a substrate in known locations and at a density of at least 1000 different probes/cm², applying a sample to obtain a hybridization pattern and comparing the pattern to a reference. The amended claims are attached as Exhibit 2.

Issues: Allegations of lack of novelty, inventive step, insufficient disclosure; and added subject matter.

References cited during Opposition and pending Appeal (by all parties, including Affymetrix):²

WO 90/15070

WO 89/10977

EP 0 063 810 A1

WO 90/05910 A1

² Applicants note that many references and declarations in relation to the opposition of EP 619 321 B1 (the '321 patent) were cited by various opposing parties, all of which are described below in relation to the '321 patent and are not repeated herein.

Drmanac, R., et al., "Sequencing by Oligonucleotide Hybridization: A Promising Framework in Decoding of the Genome Program?" The First Intl. Conf. Electrophoresis, Supercomputing, and the Human Genome, Eds. Cantor and Lim, World Scientific, pp. 47-59 (Apr. 10-13, 1990)

Ekins et al, "Development of Microspot Multi-Analyte Ratiometric Immunoassay Using Dual Fluorescent-Labeled Antibodies," *Analytica Chimica Acta* 227: 73-96, Elsevier, Amsterdam, The Netherlands (1989)

WO 92/10588

US 07/362,901

US 07/492,462

US 07/624,114

WO 90/03382

EP 0 171 150 A1

WO 84/03151

Dattagupta et al., "Rapid identification of Microorganisms by Nucleic Acid Hybridization after Labeling the Test Sample," *Anal. Biochem.* 177:85-89, Academic Press, New York, New York (1989)

Khrapko et al., "An oligonucleotide hybridization approach to DNA sequencing" *FEBS Lett.* 256(1):118-122, North-Holland on behalf of the Federation of European Biochemical Societies, Amsterdam, The Netherlands (Oct. 1989)

EP 0 392 546

WO 89/11548

McGall et al. "The Efficiency of Light-Directed Synthesis of DNA Arrays on Glass Substrates," *J. Am. Chem. Soc.* 119(22):5081-5090, American Chemical Society, Washington, D.C. (1997)

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Southern et al. "Parallel synthesis and analysis of large numbers of related chemical compounds: applications to oligonucleotides," *Journal of Biotechnology* 35:217-227 (1994)

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3. EP 0764214

Opponent(s): Clondia Chip Technologies GmbH (Germany)

Status: Opposition was filed on May 31, 2006. Response by patentee not yet filed. A copy of the Opposition is included as Form 1449 document 257.

Claims: The granted, opposed claims are generally directed to methods of packaging probe chips and packaged probe chips comprising a chip mated to a package and an alignment structure for placing the package at a desired location with respect to a scanner. The opposed claims are attached as Exhibit 3.

Issues: Allegations of lack of novelty and inventive step, allegations that the patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and that the subject matter of the patent extends beyond the content of the application as filed.

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WO 89/10977

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WO 93/22680

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US 5,320,808

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US 5,300,779

4. EP 0972564

Opponent(s): Applera Corp.

Status: The opposition was filed on February 24, 2004. A copy of the Opposition is included as Form 1449 document 259. The patentee filed a response to the opposition on January 12, 2005, a copy of which is also included as Form 1449 document 260. In response to the opposition, the EPO summoned the parties to oral proceedings as reported in the EPO Communication dated July 19, 2005, a copy of which is included as Form 1449 document 261. Opponent, Applera, withdrew its opposition on February 3, 2006. The patentee submitted further evidence in response to the summons on June 9, 2006, and a separate third party submission alleging lack of priority, novelty and inventive step was submitted on June 12, 2006. A follow-up third party submission was filed on June 30, 2006. Copies of the patentee's further submission and the third party observations are included as Form 1449 documents 262-263. The oral proceedings resulted in the EP patent being revoked. A copy of the Decision to revoke the patent and the minutes from the oral proceeding are included as Form 1449 documents 264. On October 9, 2006, the patentee filed a Notice of Appeal against the Decision of the Opposition Division. A copy of the grounds for appeal as filed on December 7, 2006 is included as Form 1449 document 265.

Claims: The granted, opposed claims are generally directed to methods of forming polymer arrays comprising a substrate and 100 or more groups of polymers with diverse, known sequences coupled to the surface thereof in discrete known locations at a density of at least 1000 per cm², wherein the known locations are separated from one another by inert regions and wherein the

polymers are delivered to the locations by spotting. The claims on appeal are attached as Exhibit 4.

Issues: Allegations of lack of novelty and inventive step, allegations that the patent lacks sufficiency, and that the patent adds subject matter over the divisional and parent applications.

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Khrapko et al., "A method for DNA sequencing by hybridization with oligonucleotide matrix," DNA Sequence – J. DNA Sequencing and Mapping 1:375-388 (1991)

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Declaration of Professor Anthony Cass, in the Opposition to EP 0972564, 17 pages (dated January 5, 2005)

Declaration of Professor John David Sutherland, in the Opposition to EP 0972564, 11 pages (dated January 4, 2005)

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5. EP 0695941

Opponent(s): Combimatrix Corporation

Status: Opposition was filed on April 28, 2003. The parties were summoned to oral proceedings to discuss the issues raised. See copy of summons, included as Form 1449 document 272. The oral proceedings were conducted on March 9, 2006, whereupon the patent was found to meet the requirements of the EPC, taking into account the auxiliary 5 amendments made at oral proceedings. A copy of the minutes of the oral proceeding and an annex of the auxiliary 5 amendments is included as Form 1449 documents 273-274.

Claims: The granted claims are generally directed to methods of making and using probe chips comprising forming a plurality of oligonucleotide arrays on a substrate, separating the substrate into a plurality of chips and mating the chips to a package comprising a reaction chamber, flowing labeled oligonucleotide target molecules through the reaction chamber wherein the package comprises an alignment structure and the package is placed at a desired location in said scanner using the alignment structure. The granted claims are attached as Exhibit 5.

Issues: Allegations of lack of novelty and inventive step, allegations that the patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and that the subject matter of the patent extends beyond the content of the application as filed.

References cited:

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6. EP 0619321

Status: Ongoing

Claims: The amended claims as published with the Notice of Grant are generally directed methods of investigating by receptor/ligand binding a sequence by the use of a substrate with a surface comprising 10^3 predefined regions containing different nucleotide or amino acid sequences, said regions each occupying an area less than about $2.5 \times 10^{-3} \text{ cm}^2$, which method comprises labeling said sequence being investigated and identifying which sequences bind with the sequence being analyzed and the corresponding apparatus. The claims are attached as Exhibit 6.

Issues: Allegations of lack of novelty, inventive step and sufficiency of disclosure.

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7. EP 0728520

Opponent(s): PamGene B.V.

Status: Opposition was filed on February 18, 2002. A copy of the Opposition is included as Form 1449 document 400. The Patentee's response to the opposition was filed on Sept. 30, 2002, a copy of which is also included as Form 1449 document 401. The parties were summoned to oral hearing to discuss the issues. The opponent then submitted further comments as to lack of novelty, inventive step and sufficiency, along with curriculum vitae for experts expected to attend the oral hearing. The additional comments are included as Form 1449 document 402. The oral proceeding concluded in the patent being revoked, as set forth in the Grounds for the Decision dated January 29, 2004, which is included as Form 1449 document 403. A Notice of Appeal was filed on April 1, 2004. The Patentee's grounds for appeal and the opponent's response are included as Form 1449 documents 404 and 405. The parties have been summoned to oral proceedings for the appeal, which are scheduled to take place on June 12, 2007.

Claims: The granted claims are generally directed to methods of deprotecting selected regions of a substrate comprising applying a deprotection agent in vapor phase to selected regions of a layer of linker molecules. The granted claims are attached as Exhibit 7.

Issues: Allegations of lack of novelty and inventive step, allegations that the patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and that the subject matter of the patent extends beyond the content of the application as filed.

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8. EP 0853679

Opponent(s): Agilent, Combimatrix, Applera and Clondia

Status: Four separate oppositions were filed by the above parties. The parties were summoned to oral proceedings to discuss the issues, however, according to the Summons, the Opposition Division preliminarily agreed with the Patentee's arguments. The summons and position of the OD is included as Form 1449 document 416. At the oral proceedings, the Opposition Division found that the amended claims submitted in the first Auxiliary Request were patentable and met all the requirements of the EPC. The minutes of the oral proceeding are included as Form 1449 document 417.

Claims: The granted claims are generally directed to methods of simultaneously monitoring the expression of a multiplicity of genes comprising hybridizing a pool of RNA transcripts to an array of greater than 100 different probes immobilized on a substrate at a density of greater than 60 different probes per cm² and attached to the surface through a single covalent bond, and quantifying hybridization by comparing hybridization of a plurality of match and control probes to provide a measure of the levels of transcription. The claims as granted by the Examination Division are attached as Exhibit 8. The claims as granted by the Opposition Division are attached as Exhibit 9.

Issues: Allegations of lack of novelty and inventive step, insufficiency of disclosure; and added subject matter.

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9. EP 0834576

Opponent(s): Dr. Peter Schneider, Abbot, PamGene, Applera, Roche Diagnostics and Combimatrix

Status: Six separate oppositions were filed by the above parties. Copies of these oppositions are included as Form 1449 documents 432-437. The Opposition of Roche Diagnostics was subsequently withdrawn. The patentee filed a response to the oppositions on February 23, 2004, which is included as Form 1449 document 438. The parties were summoned to oral proceedings, however, the Opposition Division published a preliminary non-binding opinion that the patent satisfied all the criteria of the EPC, which is included as Form 1449 document 439. Abbott submitted further observations discussing additional prior art documents. The further Abbott submission is included as Form 1449 document 440. The additional prior art documents are included in the list below. Applera submitted further observations as well as expert declarations by Southern and Wallace attesting to the state of the art of high density arrays. The further Applera submission is included as Form 1449 document 441. The expert declarations are included in the reference list below. In preparation for oral proceedings the patentee submitted declarations by Cass and Sunderland. The patentee's further observations are included as Form 1449 document 442. The expert declarations are included in the reference list below. The patentee also submitted a copy of the Opposition Division's decision in respect of EP 0834575, which was granted on

the basis of an application derived from the same patent application. This opposition is discussed elsewhere in this IDS. Following oral proceedings, the patent was revoked. The minutes of the oral proceeding are included as Form 1449 document 443. The patentee filed a Notice of Appeal on July 27, 2005. The arguments made on appeal are included as Form 1449 document 444. Applera subsequently withdrew their opposition to the patent. Abbott, Combimatrix and Dr. Schneider each filed a response to the patentee's appeal. These submissions are included as Form 1449 documents 445-447. Abbott subsequently withdrew its opposition on April 27, 2006. The appeal is currently pending.

Claims: The granted claims are generally directed to methods for detecting nucleic acid sequences in two or more collections of nucleic acids comprising contacting an array of more than 100 different probes with first and second distinguishably labeled collections of nucleic acids and detecting hybridization of the labeled complementary nucleic acids. The claims as granted by the Examination Division are attached as Exhibit 10.

Issues: Allegations of lack of inventive step; insufficient disclosure; priority of the granted patent is not valid.

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Expert Report of David Bowen Wallace, P.E., Ph.D., in the opposition to
EP 0619321, 59 pages (dated January 18, 2001)

Interlocutory decision in Opposition proceedings, from the Opposition to
EP 0834575, 39 pages (dated January 24, 2005)

[x] United States Patent and Trademark Office Interference Proceedings

Affymetrix has been a party in the following United States Patent and Trademark
Office Interference Proceedings:

1. Interference 104,358

Opponents: Incyte Pharmaceuticals, Inc. and The Board of Trustees of the Leland
Stanford Junior University

Status: Judgment was awarded against Affymetrix rendering U.S. Patent
5,800,992 invalid in view of the Order and Final Judgment of the United States
District Court for the Northern District of California in the case of Incyte
Pharmaceuticals, Inc. et al. v. Affymetrix, Inc., Case No: C99-21111 JF. A copy
of the Judgment Pursuant to Remand from United States District Court is included
as Form 1449 document 460.

Claims: The claims of the '992 patent are generally directed to a method of
detecting the relative amounts of specific targets in two differing mixtures of
nucleic acids through the use of reporter labels and hybridization within arrays.
The claims are attached as Exhibit 21.

Issues: Allegations of the lack of written description support, lack of enablement,
claim indefiniteness.

References cited:

Declaration of Ward in US 08/514,875, dated October 26, 1998

Declaration of Kricka in US 08/514,875, dated October 26, 1998

US patent application no. 07/624,114, filed December 6, 1990

US Patent No. 5,800,992

US Patent No. 5,143,854

US Patent No. 5,252,743

US Patent No. 5,744,305

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- Pirrung et al., "Comparison of Methods for Photochemical Phosphoramidite-Based DNA Synthesis," J. Org. Chem. 60:6270-6276, American Chemical Society, Washington, D.C. (1995)
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- Gait, "Chapter 1. An Introduction to Modern Methods of DNA Synthesis," pp. 1-22 in Oligonucleotide Synthesis: A Practical Approach, IRL Press Oxford (1984)
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- Atkinson and Smith, "Chapter 3. Solid-phase Synthesis of Oligodeoxyribonucleotides by the Phosphitetriester Method," pp. 35-81 in Oligonucleotide Synthesis: A Practical Approach, IRL Press Oxford (1984)
- Sproat and Gait, "Chapter 4. Solid-phase Synthesis of Oligodeoxyribonucleotides by the Phosphotriester Method," pp. 83-115 in Oligonucleotide Synthesis: A Practical Approach, IRL Press Oxford (1984)
- Schulhof et al., "The final deprotection step in oligonucleotide synthesis is reduced to a mild and rapid ammonia treatment by using labile base-protecting groups," Nucl. Acids Res. 15:397-416 (1987)
- US Patent No. 4,542,102

US Patent No. 4,711,955

US Patent No. 4,713,326

“Complain for patent infringement,” in Affymetrix, Inc. v. Synteni, Inc. and Incyte Pharmaceuticals, Inc., Civil Action No. 98-520, dated September 1, 1998

“Brief in Support of Plaintiff Affymetrix’ Motion for Preliminary Injunction,” in Affymetrix, Inc. v. Synteni, Inc. and Incyte Pharmaceuticals, Inc., Civil Action No. 98-520, dated April 15, 1999

Deposition of Sir Walter Bodmer in Patent Interference 104,358 dated July 30, 1999

Deposition of Larry Kricka in Patent Interference No. 104,358, dated May 20, 1999

Deposition of William C. Lacourse in Patent Interference No. 104,359, dated June 18, 1999

Deposition of Gail Stygall, Ph.D. in Patent Interference No. 104,359, dated June 17, 1999

Deposition of Dennis W. Solas, Ph.D.. in Patent Interference No. 104,359, dated June 16, 1999

Deposition of Martin J. Goldberg, Ph.D.. in Patent Interference No. 104,359, dated June 16, 1999

Declaration of Teresa M. Corbin in Patent Interference 104,358 dated June 15, 1999

“Oligonucleotide” pp. 349-350 in McGraw-Hill Encyclopedia of Science & Technology, 6th Edition, McGraw-Hill Book Company, New York, New York (1987)

Declaration of Professor Lubert Stryer, M.D. in European Patent No. 0 373 203 of Isis Limited and Opposition thereto by Affymetrix dated January 28, 1997

Parmalee and Kelber; “Memo to Judge Torczon re Conference Calls in Interference Nos. 104,358 and 104,359, dated June 16, 1999

2. Interference 104,359

Opponents: Incyte Pharmaceuticals, Inc. and The Board of Trustees of the Leland Stanford Junior University

Status: Involved U.S. Patent 5,744,305. A settlement agreement was reached, and the interference was terminated. Judgment was that no interference exists. A copy

of the Brown Submission under 37 C.F.R. § 1.666(b) and the Judgement Pursuant to Remand from Unites State District Court are included as Form 1449 documents 480-481.

Claims: The claims of the issued patent are generally directed to oligonucleotide arrays. The claims US 08/688,488 and the '305 patent are attached as Exhibits 11 and 12 respectively.

Issues: Allegations of improper conversion to a CIP application, lack of written description support, lack of enablement, claim indefiniteness.

References cited:

- Pirrung et al., "Comparison of Methods for Photochemical Phosphoramidite-Based DNA Synthesis," J. Org. Chem. 60:6270-6276, American Chemical Society, Washington, D.C. (1995)
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- Pease et al., "Light-generated oligonucleotide arrays for rapid DNA sequence analysis," Proc. Natl. Acad. Sci. USA 91:5022-5026, National Academy of Sciences, Washington D.C. (1994)
- Sambrook et al., "Analysis of RNA," in Molecular Cloning, A Laboratory Manual, Second Edition, Smabrook et al., Eds., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, USA, pp. 7.37-7.39 (1989)
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- Caruthers, M.H., "Gene Synthesis Machines: DNA Chemistry and Its Uses," Science 230:281-285, American Association for the Advancement of Science, Washington D.C. (1985)
- Schulhof et al., "The final deprotection step in oligonucleotide synthesis is reduced to a mild and rapid ammonia treatment by using labile base-protecting groups," Nucl. Acids Res. 15:397-416 (1987)

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Declaration of Charles L. Gholz, in U.S. Interference No. 104,359, 5 pages
(dated November 22, 1995)

Declaration of Kricka, in U.S. Interference No. 104,359, 2 pages (dated
December 3, 1998)

Declaration of Kelber, in U.S. Interference No. 104,359, 5 pages (dated
December 3, 1998)

Declaration of William C. LaCourse, in U.S. Interference No. 104,359, 14
pages (dated May 25, 1999)

Declaration of Dr. Gail Stygall, in U.S. Interference No. 104,359, 21 pages
(dated May 24, 1999)

Declaration of Sir Walter Bodmer, in U.S. Interference No. 104,359, 10
pages (dated May 27, 1999)

Declaration of Dennis W. Solas, in U.S. Interference No. 104,359, 9 pages
(dated May 28, 1999)

Declaration of Martin Goldberg, in U.S. Interference No. 104,359, 4 pages
(dated May 26, 1999)

Declaration of Teresa M. Corbin, in U.S. Interference No. 104,359, 3
pages (dated June 15, 1999)

Deposition of Larry Kricka, in U.S. Interference No. 104,359, 52 pages
(dated May 20, 1999)

Deposition of William C. LaCourse, Ph.D., in U.S. Interference No.
104,359, 22 pages (dated June 24, 1999)

3. Interference No. 104,552

Opponents: Radoje Drmanac, Radomir B. Crkvenjakov and Hyseq., Inc.

Status: A settlement agreement was reached, and the interference was terminated. Judgment that Drmanac is not entitled to priority nor to a patent. A copy of Drmanac list of intended motions included art that Drmanac was going to cite against Affymetrix is included as Form 1449 document 493.

Claims: The claims of the issued patents are generally directed to a computer program product that identifies an unknown base in a sample nucleic acid sequence. The claims of US 5,795,716 and 5,974,716 are attached as Exhibits 13 and 14 respectively.

Issues: Allegations that claims not patentable under 35 U.S.C. § 102 and/or 35 U.S.C. § 103.

References cited:

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Khrapko et al., "A method for DNA sequencing by hybridization with oligonucleotide matrix," DNA Sequence – J. DNA Sequencing and Mapping 1:375-388 (1991).

Drmanac, R., et al., Laboratory Methods--Reliable Hybridization of Oligonucleotides as Short as Six Nucleotides, DNA Cell Biol. 9:527-534, Mary Ann Liebert, New York, New York (1990)

US Patent No. 5,002,867

4. Interference 104,658

Opponents: Oxford Gene Technology, Limited

Status: A settlement agreement was reached, and the interference was terminated before filing preliminary motions. Judgment was adverse to Affymetrix; finding that it was not entitled to a patent based on claims 102, 103, and 106 of US 09/063,933. A copy of the Judgment pursuant to C.F.R. § 1.662 is included as Form 1449 document 494.

Claims: The claims of the count were generally directed to oligonucleotide arrays and methods of using said arrays to analyze polynucleotide or ligands. The claims US 6,054,270 and US 09/063,933 are attached as Exhibits 15 and 16 respectively.

Issues: None

References cited:

None; the interference was terminated before any preliminary motions were filed.

5. Interference 105,089

Opponents: Agilent Technologies, Inc.

Status: Both parties agreed to adverse judgment under 37 C.F.R. § 1.662(a). Agilent is not entitled to a patent on claims 1-18 of US 5,922,534 or claims 1-5 of US 6,255,053. Affymetrix is not entitled to a patent on claims 8-40 of US 09/614,068. A copy of the Judgment pursuant to C.F.R. § 1.662(a) is included as Form 1449 document 495.

Claims: The claims of the U.S. patents 5,922,534; 6,255,053; and U.S. application no. 09/614,068 are generally directed to oligonucleotide arrays and methods of detecting oligonucleotides and nucleic acids using arrays. The claims of US 5,922,534; 6,255,053; and US 09/614,068 are attached as Exhibits 17, 18, and 19 respectively.

Issues: Anticipation, obviousness, lack of written description support

References cited:

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Southern et al., "Analyzing and Comparing Nucleic Acid Sequences by Hybridization to Arrays of Oligonucleotides: Evaluation Using Experimental Models" Genomics 13:1008-1017, Academic Press, San Diego, California (1992)

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U.S. Patent No. 5,424,186

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Guo et al., "Direct fluorescence analysis of genetic polymorphisms by hybridization with oligonucleotide arrays on glass supports," *Nucl. Acids Res.* 22(24):5456-5465 (1994)

Eggers et al., "A Microchip for Quantitative Detection of Molecules Utilizing Luminescent and Radioisotope Reporter Groups," *BioTechniques* 17(3):516-524 (1994)

U.S. Patent No. 6,210,894

U.S. Patent No. 6,255,053

Amendment, from File History of U.S. Patent No. 5,922,534, Paper No. 4, 9 pages (dated February 11, 1997)

Office Action, from File History of U.S. Patent No. 5,922,534, Paper No. 5, 6 pages (dated May 13, 1997)

Amendment 37 C.F.R. 1.116, from File History of U.S. Patent No. 5,922,534, Paper No. 6, 7 pages (dated July 14, 1997)

Response to Office Action, from File History of U.S. Patent No. 5,922,534, Paper No. 11, 4 pages (dated October 27, 1997)

Amendment Under 37 CFR 1.116, from File History of U.S. Patent No. 5,922,534, Paper No. 14, 5 pages (dated March 13, 1998)

Resume, William C. LaCourse, 8 pages (undated)

U.S. Patent No. 5,922,534

Curriculum Vitae of James G. Wetmur, 7 pages (dated June 22, 2003)

Letter from Lauren Stevens to Deborah Neville, Esq. of Hewlett-Packard Company (with the Table of Contents of Volumes I and II attached, but without volumes I and II), 5 pages (dated July 19, 1994)

Letter from Lauren Stevens to Deborah Neville, Esq. of Hewlett-Packard Company (with the Table of Contents for the Patent Publications attached, but without the referenced binder attached), 3 pages (dated July 20, 1994)

Letter from Lauren Stevens to Deborah Neville of Hewlett-Packard Company regarding Affymetrix Technology License Agreement, 2 pages (dated July 21, 1994)

Facsimile letter from Lauren Stevens to Deborah Neville of Hewlett-Packard Company, 1 page (dated July 26, 1994)

Memo from Lauren Stevens to Affymax "Hewlett-Packard File" regarding "due diligence" (without attachment), 1 page (dated August 4, 1994)

Wetmur et al., "Light-Directed, Spatially Addressable Parallel Chemical Synthesis," Chemtracts – Biochem. Mol. Biol. 2:207-10 (1991)

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U.S. Patent No. 4,996,142

List of Affymetrix internal file numbers, 8 pages (undated)

Affymetrix Patent Portfolio – Overview, 10 pages (undated)

Declaration of James G. Wetmur, in U.S. Interference No. 105,089, 16 pages (dated June 25, 2003)

Declaration of William C. LaCourse, in U.S. Interference No. 105,089, 13 pages (dated June 26, 2003)

Declaration of Vernon A Norviel, in U.S. Interference No. 105,089, 6 pages (dated June 27, 2003)

Declaration of Lauren Stevens, in U.S. Interference No. 105,089, 7 pages (dated June 26, 2003)

Office action, from U.S. Application No 08/412,498, 8 pages, (dated October 7, 1996)

Office action, from U.S. Application No. 08/412,498, 4 pages (dated September 3, 1997)

Office action, from U.S. Application No. 08/412,498, 5 pages (dated January 21, 1998)

Office action, from U.S. Application No. 09/337,710, 5 pages (dated October 3, 2000)

Declaration of Power of Attorney for Patent Application, from U.S. Application No. 08/412,498, 1 page (dated March 28, 1995)

Notice of Appeal, from File History of U.S. Patent No. 5,922,534, Paper No. 7, 1 page (dated August 4, 1997)

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Appointment of Associate Attorney/Agent 37 CFR 1.34(b), from U.S. Application No. 08/412,498, 2 pages (dated August 4, 1997)

U.S. Patent No. 6,171,797

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Letter from Renee Lamantia to Norviel, 1 page (dated July 22, 1994)

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U.S. Patent No. 6,458,583

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Letter from Wendy Choi to Norviel regarding review of the Affymetrix patent portfolio by Hewlett-Packard, 1 page (dated August 7, 1997)

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Table of references cited by Gordon Stewart, 27 pages (undated)

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"Evaporation," in Encyclopedia of Chemistry (4th ed.), Van Nostrand Reinhold Company, New York, New York, USA, p. 366 (1984)

"Chemistry for Automated DNA/RNA Synthesis," Section 6 in Models 392 and 394 DNA/RNA Synthesizer manual, pp. 6-1 – 6-36, Applied Biosystems (1991)

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Office Action, Paper 5, Application 08/412,498, 6 pages (dated May 13, 1997)

Declaration of Henri M. Sasmor, in US. Interference No. 105,089, 15 pages (dated June 27, 2003)

Davis et al., in Basic Methods in Molecular Biology, Elsevier Science Publishing Co., Inc., New York, New York, USA, pp.62-65 and 75-78 (1986)

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Weetall et al., "Covalent coupling methods for inorganic support materials," Methods Enzymol. 44: 134-148, Academic Press, New York, New York (1976)

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U.S. Patent No. 4,563,417

U.S. Patent No. 4,994,373

Preliminary Amendment and Request for Interference Under 37 CFR 607,
Paper 2 to Application Ser. No. 09/614,068 14 pages, (dated
September 6, 2000)

Supplemental Amendment, Paper 14, to Application Serial No.
09/614,068, 10 pages (dated April 12, 2002)

Declaration of Scott M. K. Lee, in US Interference No. 105,089, 5 pages
(dated August 20, 2003)

Declaration of Salvatore J. Arrigo, in US Interference No. 105,089, 5
pages (dated August 20, 2003)

Declaration of Richard W. Evans, in US Interference No. 105,089, 4
pages (dated August 20, 2003)

- [] Publication(s) ___ listed on the attached Form PTO-1449 were cited in a foreign search or examination report corresponding to ___ application serial no. ___ and mailed on ___.
- [] Enclosed is a copy of a non-English publication(s) ___. Pursuant to §609 of the M.P.E.P., Applicant submits the attached foreign search or examination report, which cites such non-English language publication(s).
- [] Enclosed is a copy of a non-English publication(s) ___. English language publication ___ (copy enclosed) claims priority from this non-English publication.
- [x] Documents 156, 165, 166, 432, 433, 579, 596 and 608 are non-English publications. English abstracts are attached to documents 156 and 165. English abstracts may be found on the front pages of documents 596 and 608. An English abstract for document 166 may be found attached to document 165. Document 183 is an English language re-publication of the Russian original, which is attached at the end of the document. No English abstract is readily available for documents 432, 433 and 579. Applicants believe that document 432 is an opposition to EP patent 0834576. Applicants believe that document 433 is an opposition to EP patent 0834576. Applicants believe that document 579 is a publication describing the synthesis of oligonucleotides on a polymeric carrier.
- [x] The Examiner's attention is directed to related co-pending United States Patent Application Serial Nos.:
10/098,485, filed March 18, 2002, cited previously as US 2003/0104411;
10/102,774, filed March 22, 2002, cited previously as US 2002/0192684;

10/102,915, filed March 22, 2002, cited previously as US 2003/0003475;
10/098,484, filed March 18, 2002, cited previously as US 2003/0119011;
10/125,428, filed April 19, 2002, cited previously as US 2002/0155491;
10/125,460, filed April 19, 2002, cited previously as US 2002/0155492;
10/125,530, filed April 19, 2002, cited previously as US 2003/0017484;
10/694,536, filed October 28, 2003, cited previously as US 2004/0248147;
10/993,432, filed November 22, 2004, cited previously as US 2005/0112676;
10/992,782, filed November 22, 2004, cited previously as US 2005/0158743; and
10/992,772, filed November 22, 2004, cited previously as US 2005/0164249.

The following copending applications contain claims generally directed to a collection of coded beads (10/125,428); methods of analyzing expression comprising hybridizing to beads (10/125,460); and an apparatus comprising beads (10/125,530). Upon information and belief, all three applications are currently assigned to Examiner Goldberg.

This Information Disclosure Statement is filed within any one of the following time periods:

- ☐ within three months from the filing date of this national application other than a CPA under 37 C.F.R. § 1.53(d);
- ☐ within three months from the date of entry of the national stage as set forth in 37 C.F.R. § 1.491 in this international application;
- ☐ before the mailing date of a first office action on the merits; or
- ☒ before the mailing of a first office action after the filing of a request for continued examination under 37 C.F.R. § 1.114.

It is respectfully requested that the Examiner consider the above-noted information and return an initialed copy of the attached Form PTO-1449 to the undersigned. The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 50-1283.

Dated: 5-4-07

USPTO Customer No. 000033522

COOLEY GODWARD KRONISH LLP

ATTN: Patent Group

1200 19th Street, NW Suite 500

Washington, DC 20036-2412

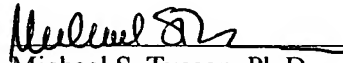
Phone: (202) 842-7800

Fax: (202) 842-7899

Respectfully submitted,

COOLEY GODWARD KRONISH LLP

By:



Michael S. Tuscan, Ph.D.

Reg. No. 43,210

Appendix A

Independent Claims of US 5,744,305:

1. An array of oligonucleotides, the array comprising:

a planar, non-porous solid support having at least a first surface; and

a plurality of different oligonucleotides attached to the first surface of the solid support at a density exceeding 400 different oligonucleotides/cm², wherein each of the different oligonucleotides is attached to the surface of the solid support in a different predefined region, has a different determinable sequence, and is at least 4 nucleotides in length.

15. An array of polynucleotides, the array comprising:

a planar non-porous solid support having at least a first surface; and

a plurality of different polynucleotides attached to the first surface of the solid support at a density exceeding 400 different polynucleotides/cm², wherein each of the different polynucleotides is attached to the surface of the solid support in a different predefined region, has a different determinable sequence, and is at least 4 nucleotides in length.

Independent Claims of US 5,800,992:

1. A method for detecting nucleic acid sequences in two or more collections of nucleic acid molecules, the method comprising:

(a) providing an array of polynucleotides bound to a solid surface, each said polynucleotide comprising a determinable nucleic acid;

(b) contacting the array of polynucleotides with:

(i) a first collection of labelled nucleic acid comprising a sequence substantially complementary to a nucleic acid of said array, and

(ii) at least a second collection of labelled nucleic acid comprising a sequence substantially complementary to a nucleic acid of said array;

wherein the first and second labels are distinguishable from each other; and

(c) detecting hybridization of the first and second labelled complementary nucleic acids to nucleic acids of said arrays.

4. A method of detecting differential expression of each of a plurality of genes in a first cell type with respect to expression of the same genes in a second cell type, said method comprising:

adding a mixture of labeled nucleic acid from the two cell types to an array of polynucleotides representing a plurality of known genes derived from the two cell types, under conditions that result in hybridization to complementary-sequence polynucleotides in the array; and

examining the array by fluorescence under fluorescence excitation conditions in which polynucleotides in the array that are hybridized to labeled nucleic acid derived from one of the cell types give a distinct fluorescence emission color and polynucleotides in the array that are hybridized to labeled nucleic acid derived from the other cell types give a different fluorescence emission color.

Independent Claims of US 5,795,716:

1. A computer program product that identifies an unknown base in a sample nucleic acid sequence, comprising:

computer code that receives a plurality of signals corresponding to probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that performs a comparison of said plurality of probe intensities to each other;

computer code that generates a base call identifying said unknown base according to results of said comparison and said sequences of said nucleic acid probes; and

a computer readable medium that stores said computer codes.

2. A computer program product that identifies an unknown base in a sample nucleic acid sequence, comprising:

computer code that receives a plurality of signals corresponding to probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that calculates a ratio of a higher probe intensity to a lower probe intensity;

computer code that generates a base call identifying said unknown base according to a base of a nucleic acid probe having said higher probe intensity if said ratio is greater than a predetermined ratio value; and

a computer readable medium that stores said computer codes.

3. A computer program product that identifies an unknown base in a sample nucleic acid sequence, comprising:

computer code that receives a first set of signals corresponding to a first set of probe intensities, each probe intensity in said first set indicating an extent of hybridization of a nucleic acid probe with a reference nucleic acid sequence, and each nucleic acid probe differing from each other by at least a single

base;

computer code that receives a second set of signals corresponding to a second set of probe intensities, each probe intensity in said second set indicating an extent of hybridization of a nucleic acid probe with said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that performs a comparison of at least one of said probe intensities in said first set and at least one of said probe intensities in said second set;

computer code that generates a base call identifying said unknown base according to results of said comparisons said sequence of said nucleic acid probe; and

a computer readable medium that stores said computer codes.

4. A computer program product that identifies an unknown base in a sample nucleic acid sequence, comprising:

computer code that receives signals corresponding to statistics about a plurality of experiments, each of said experiments producing probe intensities, each probe intensity indicating an extent of hybridization of a nucleic acid probe with a reference nucleic acid sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that receives a plurality of signals corresponding to probe intensities, each probe intensity indicating an extent of hybridization of a nucleic acid probe with said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that performs a comparison of at least one of said plurality of probe intensities with said statistics;

computer code that generates a base call identifying said unknown base according to results of said comparison and said sequence of said nucleic acid probe; and

a computer readable medium that stores said computer codes.

5. A system that identifies an unknown base in a sample nucleic acid sequence, comprising:

a processor; and

a computer readable medium coupled to said processor for storing a computer program comprising:

computer code that receives a plurality of signals corresponding to probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that performs a comparison of said plurality of probe intensities to each other; and

computer code that generates a base call identifying said unknown base according to results of said comparison and said sequences of said nucleic acid probes.

6. A system that identifies an unknown base in a sample nucleic acid sequence, comprising:

a processor; and

a computer readable medium coupled to said processor for storing a computer program comprising:

computer code that receives a plurality of signals corresponding to probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that calculates a ratio of a higher probe intensity to a lower probe intensity; and

computer code that generates a base call identifying said unknown base according to a base of a nucleic acid probe having said higher probe intensity if said ratio is greater than a predetermined ratio value.

7. A system that identifies an unknown base in a sample nucleic acid sequence, comprising:

a processor; and

a computer readable medium coupled to said processor for storing a computer program comprising:

computer code that receives a first set of signals corresponding to probe intensities, each probe intensity in said first set indicating an extent of hybridization of a nucleic acid probe with a reference nucleic acid sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that receives a second set of signals corresponding to probe intensities, each probe intensity in said second set indicating an extent of hybridization of a nucleic acid probe with said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that performs a comparison of at least one of said probe intensities in said first set and at least one of said probe intensities in said second set; and

computer code that generates a base call identifying said unknown base according to results of said comparison and said sequence of nucleic acid probe.

8. A system that identifies an unknown base in a sample nucleic acid sequence, comprising:

a processor; and

a computer readable medium coupled to said processor for storing a computer program comprising:

computer code that receives signals corresponding to statistics about a plurality of experiments, each of said experiments producing probe intensities, each probe intensity indicating an extent of hybridization of a nucleic acid probe with a reference nucleic acid sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that receives a plurality of signals corresponding to probe intensities, each probe intensity indicating an extent of hybridization of a nucleic acid probe with said sample sequence, and each nucleic

acid probe differing from each other by at least a single base;

computer code that performs a comparison of at least one of said plurality of probe intensities with said statistics; and

computer code that generates a base call identifying said unknown base according to results of said comparison and said sequence of said nucleic acid probe.

Appendix B

Independent Claims of US 5,445,934:

1. A substrate with a surface comprising 10^3 or more groups of oligonucleotides with different, known sequences covalently attached to the surface in discrete known regions, said 10^3 or more groups of oligonucleotides occupying a total area of less than 1 cm^2 on said substrate, said groups of oligonucleotides having different nucleotide sequences.

7. An array of more than 1,000 different groups of oligonucleotide molecules with known sequences covalently coupled to a surface of a substrate, said groups of oligonucleotide molecules each in discrete known regions and differing from other groups of oligonucleotide molecules in monomer sequence, each of said discrete known regions being an area of less than about 0.01 cm^2 and each discrete known region comprising oligonucleotides of known sequence, said different groups occupying a total area of less than 1 cm^2 .

Appendix C

Asserted claims of US 5,545,531:

1. A method for making a biological chip plate comprising the steps of:
 - (a) providing a body comprising a plurality of wells defining spaces;
 - (b) providing a wafer comprising on its surface a plurality of probe arrays, each probe array comprising a collection of probes, at least two of which are different, arranged in a spacially defined and physically addressable manner;
 - (c) attaching the wafer to the body so that the probe arrays are exposed to the spaces of the wells.
2. The method of claim 1 wherein the probes are DNA or RNA molecules.
3. A method for making a biological chip plate comprising the steps of providing a wafer comprising on its surface a plurality of probe arrays, each probe array comprising a collection of probes, at least two of which are different, arranged in a spacially defined and physically addressable manner; and applying a material resistant to the flow of a liquid sample so as to surround the probe arrays, thereby creating test wells.
4. The method of claim 3 wherein the probes are DNA or RNA molecules.

Asserted claims of US 5,795,716:

1. A computer program product that identifies an unknown base in a sample nucleic acid sequence, comprising:
 - computer code that receives a plurality of signals corresponding to probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by at least a single base;
 - computer code that performs a comparison of said plurality of probe intensities to each other;
 - computer code that generates a base call identifying said unknown base according to results of said comparison and said sequences of said nucleic acid probes; and
 - a computer readable medium that stores said computer codes.
5. A system that identifies an unknown base in a sample nucleic acid sequence, comprising:
 - a processor; and
 - a computer readable medium coupled to said processor for storing a computer program comprising:
 - computer code that receives a plurality of signals corresponding to probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by at least a single base;
 - computer code that performs a comparison of said plurality of probe intensities to each other; and

computer code that generates a base call identifying said unknown base according to results of said comparison and said sequences of said nucleic acid probes.

9. A system according to claims 5, 6, 7, or 8, wherein the plurality of nucleic acid probes are in an array of probes.

10. A system according to claims 5, 6, 7, or 8, wherein the plurality of probe intensities are fluorescent intensities.

Asserted claims of US 6,355,432:

2. The collection of claim 1, wherein the binding polymer is an oligonucleotide having a given length and is selected from the group consisting of all possible oligonucleotide sequences having the same number of nucleotides.

5. The collection of claim 2, wherein the oligonucleotide sequences having the same number of nucleotides are at least 5 nucleotides long.

8. The collection of claim 2, wherein the oligonucleotide sequences having the same number of nucleotides are at least 10 nucleotides long.

9. The collection of claim 2, wherein at least 10,000 of all the possible oligonucleotide sequences having the same number of nucleotides are each attached to a different single bead.

Asserted claims of US 6,399,365:

1. A package for hybridization, comprising:
a substrate comprising a first surface including a probe array with different probes comprising biological polymers immobilized on said first surface; said probe array including a density exceeding 100 different biological polymers per cm^2 ; and
a housing including a fluid cavity constructed and arranged for hybridization of a target to a probe of said probe array, said housing including a bar code.

2. A package for hybridization, comprising:
an optically transparent chip comprising a first surface including an array of probes comprising biological polymers immobilized on said first surface; and
a housing including a fluid cavity constructed and arranged for hybridization of a target to a probe of said probe array located inside said fluid cavity, said housing including a bar code and being arranged for use with a detection system.

7. A probe array deposited on a substrate, comprising:
a probe array including different probes comprising biological polymers immobilized on said substrate and having a density exceeding 100 different biological polymers per cm^2 , and
a bar code.

10. A package for supporting a probe array, comprising:
an optically transparent chip comprising an array of different probes including biological polymers, immobilized on a surface of said chip;
a housing constructed to receive said chip; and
a bar code associated with said chip.
17. The package of claim 1, 2, 8 or 10, wherein said biological polymers include nucleic acids.
20. The package of claim 1, 2, 8 or 10, wherein each of said polymers are separately located within an area of about $1\ \mu\text{m}^2$ to about $1000\ \mu\text{m}^2$.
21. The package of claim 20, wherein said nucleic acids have a density exceeding 400 different nucleic acids per cm^2 .
22. The package of claim 20, wherein said nucleic acids have a density exceeding 1000 different nucleic acids per cm^2 .
24. The package of claim 1, 2, 8 or 10, wherein said biological polymers include oligonucleotides.
27. The package of claim 1, wherein said nucleic acids have a density exceeding 400 different nucleic acids per cm^2 .
28. The package of claim 1, wherein said nucleic acids have a density exceeding 1000 different nucleic acids per cm^2 .
29. The package of claim 10 wherein said biological polymers are in fluid communication.
30. The package of claim 10 wherein said biological polymers are separately located within an area of less than $10^{-2}\ \text{cm}^2$.
31. The package of claim 10 wherein there are more than 100 different sequences in the array.
32. The package of claim 10 wherein there are more than 1000 different sequences in the array.
35. The array of claim 7, wherein said biological polymers have a density exceeding 400 different nucleic acids per cm^2 .
36. The array of claim 7, wherein said biological polymers have a density exceeding 1000 different nucleic acids per cm^2 .
37. The array of claim 7, wherein said biological polymers include nucleic acids.
41. A method of using a probe array, comprising:
providing an array of probes, comprising biological polymers immobilized on a substrate, having a density exceeding 100 different polymers per cm^2 ;
providing a bar code associated with said probe array;
reading said bar code;
aligning said probe array with a detection system; and
detecting a signal from said probe array.

44. The method of using a probe array according to claim 41, wherein said detecting said signal includes detecting a fluorescent signal emitted from said probe array.

45. The method of using a probe array according to claim 41, wherein said detecting said signal comprises scanning said probe array to quantitatively analyze said hybridization between said probes and targets.

55. The method of using a probe array according to claim 41 or 47, wherein said biological polymers include nucleic acids.

58. The method of claims 41 or 47 wherein said reading step occurs either before or after either of said aligning and detecting steps.

Asserted claims of US 6,646,243:

14. An apparatus for analyzing nucleic acid binding, comprising: a substrate that comprises at least 1000 different spheres, beads, or particles having different species of nucleic acids attached thereto, the area of the substrate containing the at least 1000 spheres, beads, or particles being less than 1 cm², at least some of the nucleic acids being bound to fluorescently labeled target nucleic acids; a laser energy source to illuminate the fluorescent labels; a detector to detect a fluorescent label bound to said target nucleic acids; and a data collection system for storing fluoresced light intensity.

15. An apparatus in accordance with claim 14 wherein the substrate comprises wells, trenches or etched regions.

16. An apparatus in accordance with claim 14 wherein the detector comprises a microscope.

18. An apparatus in accordance with claim 14 wherein the wavelength of the laser is 488 nanometers or less.

19. An apparatus in accordance with claim 14 wherein the comprises beads.

20. An apparatus in accordance with claim 14 wherein the substrate comprises spheres.

21. An apparatus in accordance with claim 14 wherein the substrate comprises particles.

22. An apparatus in accordance with claim 18 wherein the substrate or its surface may be composed of a polymer, plastic, a resin, silica or silica-based materials, carbon, metals, or inorganic glasses.

24. An apparatus in accordance with claim 18 wherein the substrate or its surface may be composed of silica.

26. An apparatus in accordance with claim 14 wherein there are 10,000 different spheres, beads, or particles.

35. A method for screening large numbers of biological polymers, comprising: providing target nucleic acids; providing a substrate having an array of at least 1000 different beads, the different beads occupying

an area on a substrate of less than 1 cm^2 , at least some of the different beads having different nucleic acids covalently attached thereto; contacting the target nucleic acids and the beads so that after contact at least some of the nucleic acids on the beads hybridize to the target nucleic acids further comprising having fluorescently labeled nucleic acids bound thereto; illuminating the array with a laser energy source to excite the fluorescent labels; and detecting fluoresced light with a detector that is connected to a data storage system; and determining which nucleic acids on the beads have bound to target nucleic acids.

36. A method in accordance with claim 35 wherein the detector comprises a microscope.

39. A method in accordance with claim 35 wherein the fluorescent label is attached to the target nucleic acid before contact with the beads.

40. A method in accordance with claim 35 wherein the nucleic acids bound to the beads are oligonucleotides.

43. A method in accordance with claim 35 wherein the detector acquires data every 0.8 to 10 microns.

Asserted claims of US 6,607,887:

1. A method of identifying an unknown base in a sample nucleic acid sequence, comprising: inputting probe intensities for a plurality of nucleic acid probes that differ by a base at an interrogation position corresponding to the unknown base, each probe intensity indicating hybridization affinity between a nucleic acid probe and the sample nucleic acid sequence; analyzing the probe intensities and at least one probe intensity from a nucleic acid probe with an interrogation position corresponding to a position near the unknown base in the sample nucleic acid sequence; and generating a base call identifying the unknown base according to results of analyzing the probe intensities and the at least one probe intensity.

5. The method of claim 1, wherein the position near the unknown base in the sample nucleic acid sequence is adjacent to the unknown base.

7. A computer program product that identifies an unknown base in a sample nucleic acid sequence, comprising: computer code that receives probe intensities for a plurality of nucleic acid probes that differ by a base at an interrogation position corresponding to the unknown base, each probe intensity indicating hybridization affinity between a nucleic acid probe and the sample nucleic acid sequence; computer code that analyzes the probe intensities and at least one probe intensity from a nucleic acid probe with an interrogation position corresponding to a position near the unknown base in the sample nucleic acid sequence; computer code that generates a base call identifying the unknown base according to results of analyzing the probe intensities and the at least one probe intensity; and a computer readable medium that stores the computer codes.

INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)

PTO Form 1449

Attorney Docket No.
AFFY-003/26US

Application No.
10/694,541

Applicants: Stephen P.A. FODOR *et al.*

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Filing Date: October 28, 2003

Group Art Unit: 1634

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